6-22-04 AF/1651 IFW

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Maingault, P. *et al.* Group Art Unit: 1651

Application No.: 09/364,908 Examiner: Witz, J.C.

Filed: July 27, 1999 Attorney Docket No.: 43869.016200

For: SYSTEM FOR TREATING WOUNDS AND METHOD FOR PRODUCING THIS SYSTEM

MAIL STOP APPEAL BRIEF-PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 17 to 35 which are all of the claims pending in this application.

REAL PARTY IN INTEREST

This application is assigned to Les Laboratoires Brotherier.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences.

STATUS OF THE CLAIMS

The instant application was filed continuing original claims 1 to 16. Claims 1 to 16 were cancelled and replaced with claims 17 to 35. In the amendment filed on March 18, 2002, claim 17 was amended. Pending claims 17 to 35 are the claims on appeal in this

appeal. A copy of the pending claims is attached as appendix A, hereto.

STATUS OF AMENDMENTS

Appellant's response to the final rejection has been entered by the Examiner.

SUMMARY OF THE INVENTION

The invention to a treatment intended for the care of patches of necrosis, acute surgical wounds and other types of wounds. (p.1, l. 1-2).

More specifically, the invention relates to a method using a natural wound-treatment system wherein the system adapted to change state in a reversible manner by passing from the gel state to the solution state and vice-versa, having polysaccharide macromolecules and aliphatic chains attached to a single polysaccharide macromolecular (p.2, l. 10-13).

The invention can understood with the aid of the following description of different embodiments of the wound-treatment system and of different embodiments of the method for producing the treatment system, with reference to the attached drawing which:

-Figure 1 illustrates three macromolecules of the treatment system in the gell state, according to one particular embodiment;

-Figure 2 illustrates stages of the method for producing the treatment system according to one of the embodiments;

-Figure 3 illustrates the treatment system in which molecules of an active principle are trapped before the active principle.

-Figure 4 illustrates the treatment system of Figure 3 during the release of the active principle;

-Figure 5 illustrates the treatment system in which living cells are trapped before these cells are released, and

-Figure 6 illustrates the treatment system of Figure 5 during release of the cells (p. 4, l.

8-20).

In the particular example of the invention each aliphatic chain 11-15, 21-24, 31-33 is provided with a single attachment group, in this case an ionized amine group NH_3^+, by means of which it is attached to a single alginate macromolecule 10, 20, 30 by a chemical bond consisting of an ionic bond between the ionized amine group NH_3^+ and an ionized carboxylate group COO- of the alginate macromolecule.

The aliphatic chains 11-15, 21-24, 31-33 of each macromolecule 10, 20, 30 form hydrocarbonic arms which – when the system is in the gel state – are associated with hydrocarbonic arms of at least one other neighbouring macromolecule. In Figure 1 it is possible to see that the hydrocarbonic arms of each of the macromolecules 10 (20; 30) are associated with hydrocarbonic arms of the two other macromolcules 20, 30 (10, 30; 10, 20). Each association of hydrocarbonic arms ahs a number m of hydrocarbonic arms, m being a natural number greater than or equal to two. The hydrocarbonic arms 11/21, 12/22/13, 14/32/15/33, 23/31/24 of each association of arms are linked to each other by physical bonds consisting of hydrophobic interactions. The alginate macromolecules 10, 20, 30 are thus associated with each other by means of their hydrocarbonic arms 11-15, 21-24, 31-33.

The hydrophobic interactions between the associated arms 11/21, 12/22/13, 14/32/15/33, 23/31/24 of the macromolecules 10, 20, 30 have an energy which is both sufficiently great to ensure sufficient strength for the system in the gel state, and sufficiently weak to permit this gel to pass into the solution state under the effect of external forces such as the temperature, mechanical forces, pH, ionic strength, etc. Moreover, this change of state is reversible. In other words, under the effect of external forces, the system can pass form the gel state to the solution state by separation of the associated hydrocarbonic arms 11/21, 12/22/13, 14/32/15/33, 23/31/24 and, conversely, from the solution state to the gel state by association of the hydrocarbonic arms 11-15, 21-24, 31-33.

In this way it is possible, in particular, to pour the alginate system in the solution state onto the wound to be treated so that it conforms to the shape of the wound and comes into close contact with it. After a setting time the system gels and so adheres closely to the wound without the risk of running. Then under the effect of the ionic strength of the biological tissue medium and/or of the pH thereof, alginate gel located in the proximity of the wound liquefies so that in spite of possible mechanical forces (changes in the wound, movement of the patient) the close contact between the treatment system and the wound will always be maintained (p. 5, l. 2, to p.6, l. 8).

ISSUES ON APPEAL

Are claims 17 to 35 unpatentable under 35 U.S.C. §103(a) over Francesco et al. (Francesco) combined with WO 96/37519 (WO '519)?

GROUPING OF THE CLAIMS

Appellants concede that all of the pending claims stand or fall together.

ARGUMENT

The present invention is directed to a method for treatment of a necrosis or wound comprising preparing a wound-treatment product, adapted to change state in a reversible manner from a solution state to a gel state and from a gel state to a solution state, the product comprising aliphatic chains attached to a polysaccharide macromolecules, wherein each aliphatic chain is attached to a single polysaccharide macromolecule. The wound-treatment product is applied in the solution state to a necrosis or wound, and the state of at least a portion of the product is changed from the solution state to the gel state.

In contrast, Francesco discloses a procedure for the preparation of alginic esters by

treating quaternary ammonium salts of alginic acid with conventional alkylating agents in organic solvents. Column 4, lines 15 to 20. Francesco does not disclose a method for treatment of a necrosis or wound, where a wound-treatment product is applied in the solution state to a necrosis or wound, and the state of at least a portion of the product is changed from the solution state to the gel state.

WO '519 discloses a polysaccharide hydrogel material consisting of a crosslinked product of a fuctionalized derivative of alginic acid or hyaluronic acid in which a portion of the carboxylic acid groups are partially satisfied with an unsaturated aliphatic or aliphatic alcohol, and the remaining carboxylic groups are partially salified with a cation. The functionalized acid is subjected to UV, gamma, or β radiation to form the hydrogel (page 2, lines 2 to 13).

WO '519 does not disclose a method for treatment of a necrosis or wound comprising preparing a wound-treatment product, and applying the wound-treatment product in the solution state to a necrosis or wound, and changing the state of at least a portion of the applied production from the solution state to the gel state.

Francesco is directed toward the field of ophthalmology. The Examiner accurately noted that the compositions of Francesco are described as being used for ophthalmological application where excellent adhesion to the corneal epithelium is desired. For this reason, Francesco does not disclose the instant method, i.e., preparing a solution: A) changing the solution into a gel state, and B) changing the gel into a liquid state.

Nowhere does Francesco disclose a reversible product. The solution of Francesco is a polysaccharide with a high degree of esterification. It is not hydrosolugilizable. Bringing the solution of Francesco into contact with an aqueous solution does not mean that it is or that it becomes solubilized. What does happen is that it is dispersed throughout the solution. But, if the solution of Francesco were to be solubilized, it could not be used in an ophthalmological

application because the liquid solution could change the optical properties of the eye. In an ophthalmological application, our disclosed and claimed process should be avoided. Clearly, Francesco does not disclose or even suggest doing the series of steps which we disclose and claim as our invention.

The claims on appeal refer to a method for treatment of a necrosis or wound and a main feature of the instant invention is the reversibility of the gel which is composed of aliphatic chains attached to polysaccharide macromolecules.

Reversibility has as an advantage the possibility of applying the treatment product to a wound in a liquid state so that it spreads over the wound, conforms to the shape of the wound, sets to a gel and can liquefy again when it is close to the wound because of body heat or ionic strength. This feature is an important one and these elements are recited in new claim 17 which is a combination of old claims 17 and 18.

Reversibility depends on the nature of the cross links between macromolecules. In the present invention one forms physical gels. A description of this kind of gel is given in the attached article "Biodegradable hydrogels for drug delivery" pages 99 and 100. The gels are caused by multiple weak junction zones between the aliphatic chains of different macromolecules, see line 4 at page 5 of the present specification referring to hydrophobic interactions between the associated arms. (Also mentioned in "Macromolecular complexes... " and the article "Amphiphilic derivatives of sodium alginate.... " hereto attached).

These bonds differ from the strong chemical gels. Moreover there is a relationship between reversibility and substitution rate, i.e., extent of esterification. In the examples of the specification at pages 7, a level of substitution of the order of 8% is given.

Another feature of the invention are the highly effective intrinsic natural curative properties of the system to be found in the aliphatic chains. Additional molecules of an active

principle may be trapped inside the alveoli but it is not compulsory for obtaining the curative effect.

Francesco discloses the general medical, surgical, cosmetic and food use of esters of alginic acid (abstract). This citation covers a very large scope of products and uses but there is no information relating to the present invention.

The Examiner refers to the ophthalmological application, col. 16. It is to be noted that Francesco only discloses that an amorphous powder on contact of the tissue constitutes a concentrated aqueous solution of a gelatinous character with viscous consistency and elastic properties. There is no indication of reversibility. There is a passage from a anhydrous solid state to a gel state. Francesco does not teach the use of a reversible gel. In fact a reversible gel would not be suitable because it would liquefy and would make vision indistinct.

Therefore, Francesco teaches the use of irreversible gels.

This is confirmed at col. 12 lines 58-62: "*for the manufacture of sanitary surgical articles it s preferable to use total or partial esters with a high grade of esterification, for example between 80% and 100% of all the carboxy groups present.* The citation refers at lines 63-68 to a wide interval between 5% and 90% but is for a very broad group of purposes comprising alimentary, cosmetic and pharmaceutical. One can conclude that for the ophtalmological use the reference intends a gel with at least 80% esterification grade that is certainly not reversible.

It should be pointed out that the WO citation refers to chemical gels. At page 3 lines 20-24: "the new compounds present a compact, three dimensional structure (wall to wall) the latter are therefore characterized by greater mechanical resistance".

This new compound is to be opposed to "the gels constituted by inner esters of haluronic bound together by simple, physical-type bonds" (page 3, lines 18-20).

The gels of the present invention should be placed in the second category. They have a weak bond. Because of the weak nature of the bond they are reversible.

On the contrary such a feature does not belong to the gels of WO that are reversible. The process includes the step of "subjecting the article to radiation selected from the group consisting of UV, beta or gamma radiation" page 7 lines 5-6. The applications as film membranes, fibers or threads (page 6) are clearly not the kind of use that is claimed where the product is poured in a liquid state into the wound or necrosis.

It is urged that the cited references by the Examiner do not teach the use of a product that is first in a solution state then in a gel state and that will liquefy again proximate to the tissue of the wound under external strains such as body heat or ionic strength.

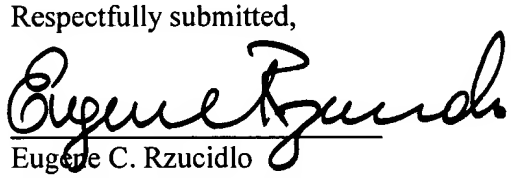
CONCLUSION

Appellant urges for the reasons given above that the present claims are allowable over the applied prior art. The Examiner is requested to reconsider the §102 and §103 rejections and withdraw these rejections.

If the Examiner maintains these rejections, appellant respectfully request that the Board reverse the Examiner's §102 and §103 rejections.

Dated: 06/21/09

Respectfully submitted,

By: 

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